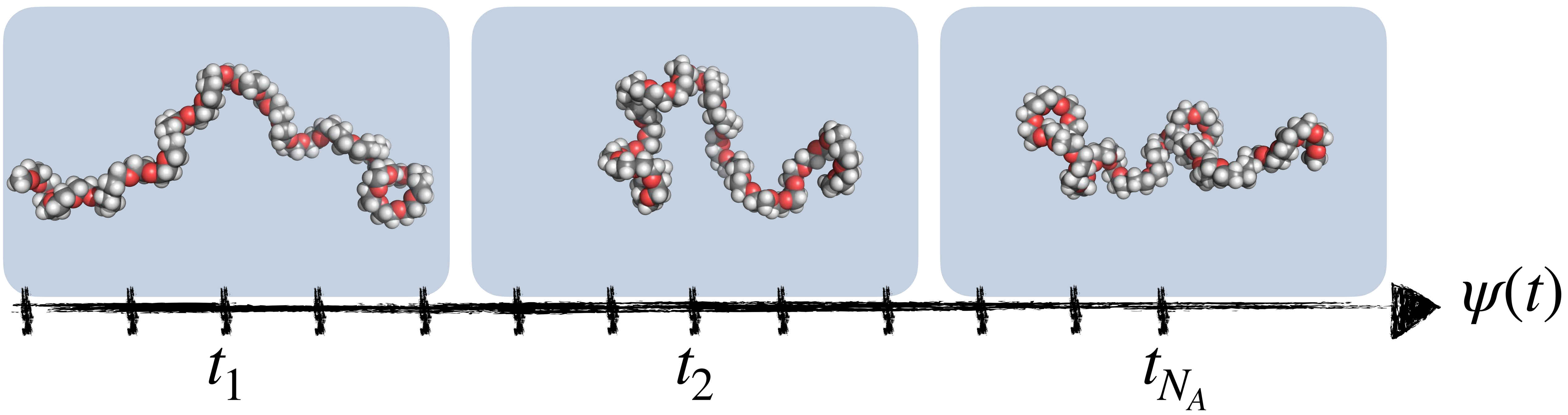
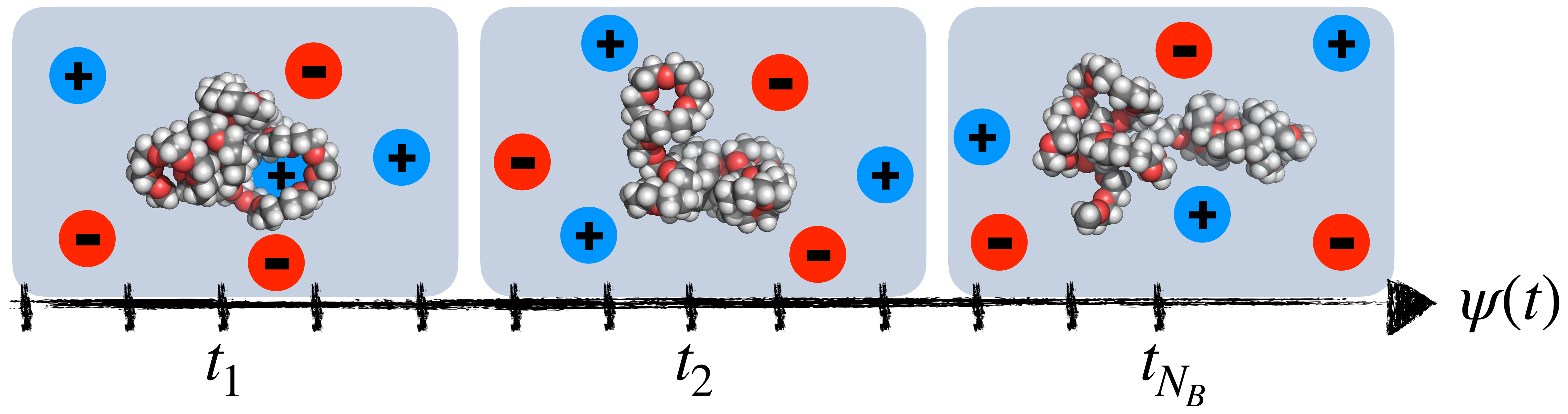
Step 1: Generation of ensembles of solute structures ψ

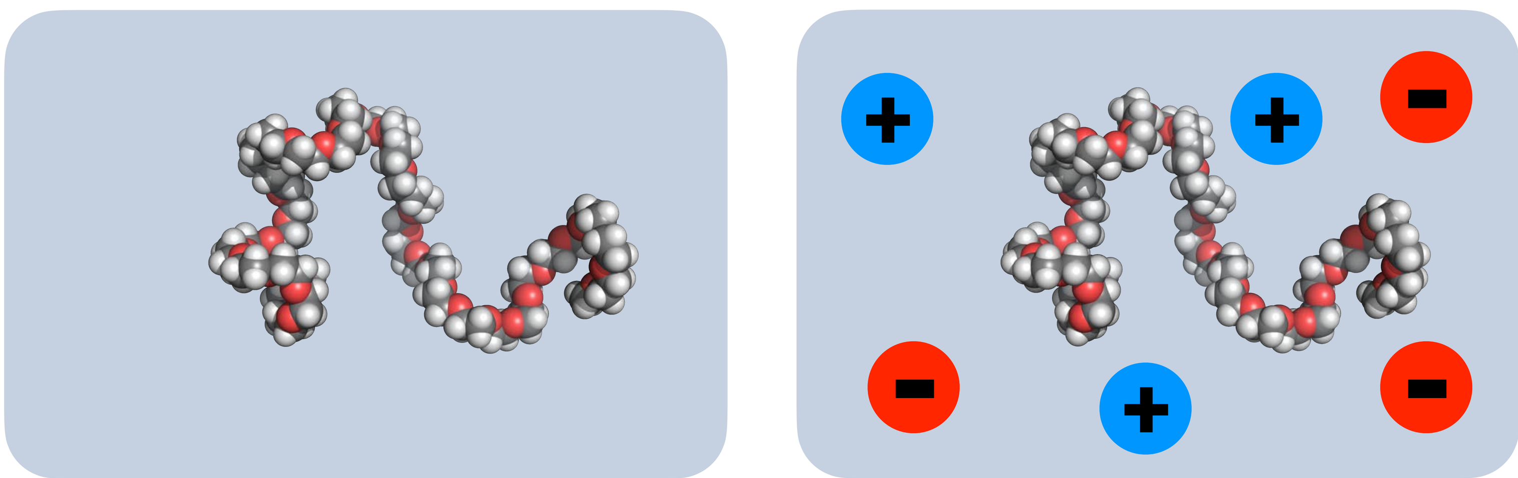
Generation of $P_A(\psi)$



Generation of $P_B(\psi)$

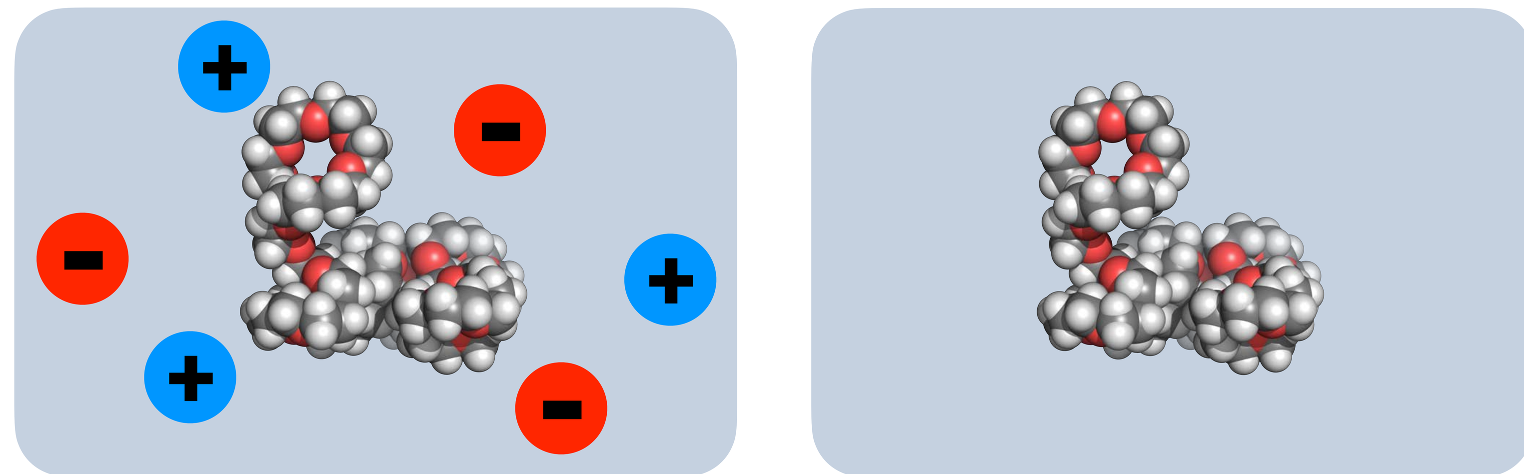


Step 2: Generation of solvent configurations in presence of rigid solute



$\nu_A^{\mathrm{solv}}(\psi)$ $\quad$ $\nu_B^{\mathrm{solv}}(\psi)$

$$\Delta\nu^{\mathrm{solv}}(\psi) = \nu_B^{\mathrm{solv}}(\psi) - \nu_A^{\mathrm{solv}}(\psi)$$



$\nu_B^{\mathrm{solv}}(\psi)$ $\quad$ $\nu_A^{\mathrm{solv}}(\psi)$

$$\Delta\nu^{\mathrm{solv}}(\psi) = \nu_B^{\mathrm{solv}}(\psi) - \nu_A^{\mathrm{solv}}(\psi)$$

Step 3: Calculations of $\Delta\mu^{\mathrm{ex}}$ and its upper and lower bounds

$$\sum_{\psi\in A} \mathscr{F}\left(\Delta\nu^{\mathrm{solv}}(\psi) - \Delta\mu^{\mathrm{ex}}\right) = \sum_{\psi\in B} \mathscr{F}\left(-\Delta\nu^{\mathrm{solv}}(\psi) + \Delta\mu^{\mathrm{ex}}\right)$$

$$\Delta\mu^{\mathrm{ex}}_{\mathrm{upper}} = \frac{1}{N_A}\sum_{\psi_i\in A, i=1}^{N_A} \Delta\nu^{\mathrm{solv}}(\psi_i)$$

$$\Delta\mu^{\mathrm{ex}}_{\mathrm{lower}} = \frac{1}{N_B}\sum_{\psi_i\in B, i=1}^{N_B} \Delta\nu^{\mathrm{solv}}(\psi_i)$$